Rejections under 35 USC § 112 ¶ 2:

Claim 41 stands rejected as being indefinite, for recitation of hybridization under stringent conditions.

Applicant respectfully disagrees. The term "stringent hybridization conditions" is defined on page 188 of the specification. For convenience of the reader, by way of this Amendment, the conditions are now explicitly indicated in the claim. This does not introduce any new limitation, because the meaning of the term was already implicitly understood. Withdrawal of this rejection is requested.

Claims 43, 47, 50, and 56 stand rejected as being indefinite, on the basis that there needs to be an activity with which the "increased level" of telomerase activity is compared.

Applicant respectfully disagrees. The skilled reader would realize that the telomerase activity will be increased as a result of having conducted the method on the cell, in comparison to the level of telomerase activity had the method not been conducted on the cell. For convenience of the reader, by way of this Amendment, this is now explicitly indicated in the claim. The amendment does not further limit the claim, because the meaning was already implicitly understood. Withdrawal of this rejection is requested.

Claims 41-57 stand rejected as being incomplete for omitting steps. Specifically, the Office Action indicates that the claim does not contain the step of determining the proliferative capacity of the cell.

Applicant respectfully disagrees that it is necessary to recite this step in the claim. The skilled reader will readily understand that proliferative capacity of a cell can be determined simply by culturing it under conditions suitable for proliferation until it stops proliferating. A cell that proliferates longer as a result of conducting the claimed method will have increased proliferative capacity.

However, there is no need for the user to incur the time delay and expense of determining proliferative capacity of the cell in order to practice the invention, unless of course they desire to do so. Ordinarily, the user will simply express the hTRT polynucleotide in the cell, with the understanding that as a result, the cells will inherently have increased proliferative capacity.

By way of this Amendment, claim 41 has been reworded to indicate that introducing the recombinant polynucleotide into the cell increases the proliferative capacity of the cell. The new wording does not introduce a new limitation, but it connects the result of performing the introducing step with the result indicated in the preamble. Withdrawal of this rejection is requested.

Rejections under 35 USC § 112 ¶ 1:

Claim 41 and its dependents stand rejected under this Section as containing subject matter not described in the specification. The Office Action indicates that there are no working examples showing that increasing TRT expression in mortal mammalian cell would cause them to become immortal. Published articles by Kiyono et al. (Nature 396:84, 1998) and O'Hare et al. (Proc. Natl. Acad. Sci. USA 98:646, 2001) are cited as standing for the proposition that immortalization by expression of hTRT alone is probably cell-type specific.

Applicants disagree with this rejection for a number of reasons:

1. It is not necessary for applicants to have a working example in the specification in order for the specification to meet the description and enablement requirements of 35 USC § 112 ¶ 1. A specification can adequately describe the manner and process of making an embodiment of an invention, whether or not it has actually been conducted. Use of prophetic examples does not make a patent non-enabling. The burden is on the person challenging the patent to show that the prophetic examples together with other parts of the specification are not enabling. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984).

2. The claims in this application do not require that the cells treated according to the method proliferate indefinitely — only that they have *increased proliferation capacity*. While some telomerized cells may indeed become immortal, it is not required that they necessarily be immortal in order to meet the limitations of the claimed invention.

3. The references cited in the Office Action actually demonstrate that the claimed invention *works*. O'Hare et al. state on page 651, col. 1: "Although ectopic expression of [TRT] alone resulted in extension or stabilization of telomeres, this activity was not sufficient for immortalization of these cells in our hands. *Some extension of growth potential was observed with both cell types* . . .". Kiyono et al. say on page 87, col. 2: "We found that [TRT] extended the lifespan of primary [human foreskin fibroblasts] by at least 70 population doublings." Kiyono et al. reported that additional manipulations were needed to immortalize their keratinocyte preparation under the conditions they studied. However, there is evidence elsewhere that TRT expression is sufficient to extend the proliferative capacity of several lines of primary keratinocytes under appropriate culture conditions. See U.S. Patent application 60/289,903, and Ramirez et al., Genes Dev. 15:398, 2001, both of which are enclosed.

4. To meet the requirements of 35 USC § 112 ¶ 1, it is not necessary that expressing TRT in cells cause them to have increased proliferative capacity *in all instances.* Claims can be enabled by the specification even if they read on inoperative embodiments. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984). In fact, the claims of the present application do not read on inoperative embodiments, since the claimed method requires that the proliferative capacity of the cell be increased as a result of introducing the polynucleotide.

5. The invention can be practiced without undue experimentation, because a reasonable proportion of cell lines introduced with the polynucleotide will have their proliferation capacity enhanced as a result of expressing TRT.

There is plenty of published evidence that this is so. For example, Bodnar et al. (Science 279:349, 1998) transfected two telomerase-negative normal human cell types (retinal pigment epithelial cells and foreskin fibroblasts) with vectors encoding TRT, as described in this application. In contrast to telomerase-negative control clones, which exhibited telomere shortening and senescence, telomerase-expressing clones had elongated telomeres, divided vigorously, and showed reduced straining for beta-galactosidase, a biomarker for senescence. The telomerase-expressing clones had a normal karyotype and reportedly exceeded their normal proliferative capacity by at least 20 doublings. Bodnar et al. also demonstrated that vascular endothelial cells transfected with hTRT also have increased proliferative capacity.

Accompanying this amendment is a review article by Calvin B. Harley, Chief Scientific Officer of Geron Corporation. Table 1 shows a survey of a number of different cell lines. The survey shows that TRT *typically does increase replicative capacity* in a wide variety of cell lines when tested under appropriate culture conditions.

In Figure 2, Dr. Harley explains that normal somatic cells transduced to express TRT will not reach the Hayflick limit (line b, bottom panel). TRT expressing cells may still be susceptible to the trauma or culture shock checkpoint — but if they bypass this, they will continue to proliferate beyond the replicative limit normally caused by telomere shortening. Indeed, this patent application does not require that telomerized cells will be completely impervious to poisons, fires, snow storms, and all other traumatic assaults. And so it is expected that not all cell lines cultured under all conditions will show increased proliferation as a result of TRT expression.

However, as illustrated in the reference by Bodnar et al. *(supra),* and confirmed in Table 1 of Dr. Harley's review, a generous proportion of cell lines treated to express TRT show substantially increased proliferative capacity.

For any and all of these reasons, applicant respectfully submits that the claimed invention is described in the specification as required under 35 USC § 112 ¶ 1. Withdrawal of this rejection is requested.

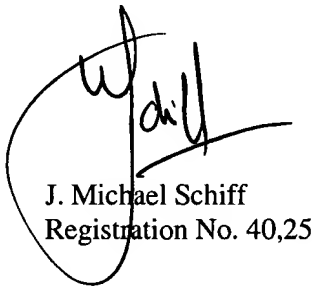
Conclusion

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and an early Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief. The Assistant Commissioner is hereby authorized to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139.

Respectfully submitted,



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Version with Markings to show

CHANGES MADE

USSN 09/432,503
Docket 018/063c

Amended Title:

~~HUMAN TELOMERASE CATALYTIC SUBUNIT~~

INCREASING THE PROLIFERATIVE CAPACITY OF CELLS USING TELOMERASE REVERSE TRANSCRIPTASE

Amendments to Claims:

41. A method of increasing the proliferative capacity of a mammalian cell, comprising introducing into the cell a recombinant polynucleotide ~~comprising a nucleic acid sequence~~ that encodes a telomerase reverse transcriptase protein, variant, or fragment having telomerase catalytic activity when complexed with a telomerase RNA,

~~wherein the polynucleotide hybridizes under stringent conditions to a polynucleotide having a sequence complementary to SEQ ID NO:1, and~~

wherein DNA having the sequence of the polynucleotide hybridizes to DNA having the sequence of SEQ. ID NO:1 at 5°C to 25°C below T_m in aqueous solution at 1 M NaCl;
wherein T_m is the melting temperature of double-stranded DNA having the sequence of SEQ. ID NO:1 under the same reaction conditions; and

~~wherein the expression of the hTRT protein from the recombinant polynucleotide in~~

whereby introducing the recombinant polynucleotide into the cell increases the proliferative capacity of the cell.

42. The method of claim 41, wherein the cell is a human cell.

43. The method of claim 41, further comprising selecting ~~cells that express an increased level of~~ the cell because it expresses increased telomerase catalytic activity as a result of introducing the polynucleotide.

44. The method claim 43, wherein the cell is a human cell.

45. The method of claim 41, wherein the polynucleotide encodes a full-length, naturally occurring telomerase reverse transcriptase.

46. The method of claim 45, wherein the cell is a human cell.

47. The method of claim 41, further comprising selecting ~~cells that express an increased level of~~ the cell because it expresses increased telomerase catalytic activity as a result of introducing the polynucleotide.

48. The method of claim 41, wherein the polynucleotide encodes a telomerase reverse transcriptase having the amino acid sequence of SEQ ID NO:2.

49. The method of claim 48 wherein the cell is a human cell.

50. The method of claim 48 further comprising selecting ~~cells that express an increased level of~~ the cell because it expresses increased telomerase catalytic activity as a result of introducing the polynucleotide.

51. The method claim 50 wherein the cell is a human cell.

52. The method of claim 41, wherein the recombinant polynucleotide is an expression vector.

53. The method of claim 52 wherein the expression vector is an SV40 virus expression vector, an EBV expression vector, an *Autographa california* nuclear polyhedrosis virus expression vector, a herpesvirus expression vector, or a vaccinia virus expression vector.

54. The method of claim 52 wherein the expression vector is a retrovirus expression vector.

55. The method of claim 52 wherein the expression vector is an adenovirus expression vector.

56. The method of claim 52 further comprising selecting ~~cells that express an increased level of~~ the cell because it expresses increased telomerase catalytic activity as a result of introducing the polynucleotide.

57. The method claim 52 wherein the cell is a human cell.